REMARKS

After entry of the present amendment, claims 94 to 111, 133, and 136 to 141 are pending. Claims 94 and 110 are the pending independent claims.

Claims 94-111, 133, 138-141 stand rejected under 35 U.S.C. § 103(a) as being obvious over Smit et al. (Biochemical and Biophysical Research Communications, 1992, Vol. 187) (hereinafter "Smit I") in view of Smit et al. (Electrophoresis, 1994, Vol. 15, pp. 251-254) (hereinafter "Smit II"). Applicant respectfully requests reconsideration and allowance in view of the remarks herein.

The claimed invention is directed to the introduction of desired properties with minimal changes to the structure. The claimed invention further provides the performance of quantitative structure function analysis using gradually increasing modification, monitoring this modification, and using protease treatment and mass spectrometry and assaying biological activity. Protease treatment and mass spectrometry are carried out to locate and determine the nature of the modification(s).

Pending independent claim 94 requires gradual chemical modification of a protein or peptide specifically directed to the catalytic activity center of the protein or peptides without distortion of the receptor binding center. The generic disclosure of "enhanced biological activity" by Smit II does not provide or suggest evidence of position specific modification in which a molecule's catalytic activity is modified without distortion of the binding center of the IL-3 receptor. Similarly, Smit I's discussion of IL-3 modification for the study and localization of zinc binding does not provide or suggest evidence of position specific modification in which a molecule's catalytic activity is modified without distortion of the binding center of the IL-3 receptor.

Pending independent claim 110 includes the following limitation: "wherein the human interleukin 3 is modified only at one or more of the following residues: Ala^{1}, His^{26}, Lys^{28}, Lys^{66}, His^{95}, His^{98}, Lys^{100}, or Lys^{116}." Neither Smit I nor Smit II teach any modification of His residues. Moreover, neither Smit I nor Smit II teaches position specific Lys modifications.

While Smit I describes Lys modification, it does not describe any position specific modification. Instead, at best Smit I only described the deducement of the number of modifications per molecule.

In regard to the Examiner's statement that "Smit [II] teaches gradual chemical modification of IL-3 by alkylation with acetic anhydride and proteases..." (Office action at page 4, lines 5-6), Applicant respectfully submits that Smit II describes acylation with acetic anhydride, not alkylation.

In regard to the Examiner's comment at page 5 of the Office Action (lines 8-12), the Examiner contends that the skilled artisan would envisage assaying the biological activity of the chemically modified IL-3 because the purpose of IL-3 modification is to alter its biological activity. Applicant respectfully submits that one of ordinary skill in the art would, in fact, not be motivated to assay the biological activity for the following reasons. First, in Smit I, the IL-3 modification was used to study and localize zinc binding. In Smit II, the IL-3 modification was used to study an electrophoresis protocol. Modification of cytokines can also be used to investigate the spatial structure of cytokines (e.g., chemical cross-linking) and accessibility of residues from the environment. Modification has also been used in the art to find epitopes of antibodies. Indeed, numerous other applications can be contemplated for the modification of cytokines which have no bearing on biological activity.

Accordingly, the claimed invention would not be obvious to one of ordinary skill with regard to testing the biological activity.

In regard to certain of the dependent claims, we make the following distinctions.

Specifically in regard to claim 107, neither Smit I nor Smit II teaches or suggests modification of His-residues.

Specifically in regard to claim 139, the Examiner states that "it is noted that it is expected that the modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by the claims, absent any evidence to the contrary." (Office Action, page 3.) Applicant respectfully submits that the Examiner's assumption is incorrect for the following reasons.

First, Smit I discloses treatment with Endo Lys-C, which results in a peptide consisting of 11-28 S-S 80-100. (Smit I at Figure 4, page 864.) This peptide still has zinc-binding capacity.

Second, Smit I discloses treatment with Carboxypeptidase Y to generate peptides by degradation from the C-terminus. (Smit I at page 862.) In the pending application, it was demonstrated that Lys116 is important for biological activity. (Publication of pending application at ¶¶ [0127]-[0128].) The Klein et al. reference (J. Biol. Chem., 272(36): 22630 (1997)) shows that Glu-43 and Lys116 form an important part of the receptor binding site of IL-3.

The zinc binding fragment 11-28 S-S 80-100 still has zinc binding capacity. Therefore, any species obtained with Carboxypeptidase Y would first remove the Lys116 (receptor binding) before getting to the zinc binding area. Therefore, Carboxypeptidase Y treatment would indicate that there is no possibility to selectively remove zinc binding. This suggests that receptor binding is more likely to be harmed than zinc binding and therefore provides a compelling showing that it is not likely that antagonistic activity can be expected after modification according to Smit I. Smit II does not concern either receptor binding or zinc binding. This clearly demonstrates that one of ordinary skill in the art would not expect that the Carboxypeptidase Y-modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by claim 139.

Additionally, the zinc binding fragment 11-28 S-S 80-100 can be generated with complete Endo Lys-C and still have zinc binding capacity. This Endo Lys-C fragment contains neither Asp^{43} nor Lys^{116}. Thus, the Endo Lys-C treatment would indicate that modification of the receptor binding site is considerably more likely than the likelihood of selective modification of the zinc binding site without harming the receptor site. This demonstrates that one of ordinary skill would not expect that the Endo Lys-C modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by claim 139.

Because both Carboxypeptidase Y and Endo-Lys C treatment showed that the receptor binding site is preferably modified instead of the zinc binding site, and the remaining proteases of Smit I did not result in interpretable data, Applicant respectfully submits that this

is evidence that one of ordinary skill would not expect that modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by claim 139.

Applicants also respectfully submit another reason that one of ordinary skill in the art would not expect that modified IL-3 would have the properties to inhibit native IL-3 based on the cited references. Cytokines, like IL-3, are very complex molecules and the receptor binding site is easily disrupted, such as by any protease treatment that results in cleavage within the receptor binding site. For the generation of an effective antagonist, it is necessary that the catalytic center is almost completely disengaged while the receptor binding center is almost completely unharmed or even improved.

For example, native IL-3 is a molecule of about 133 amino acids. Complete digestion of the molecule (e.g., with pronase) to individual amino acids does not result in any signaling molecules, nor does it result in antagonists. Similarly, complete digestion of the molecule to dipeptides or to tripeptides does not provide any signaling molecules, nor does it result in antagonists. Accordingly, many protease treated products will result in inactive molecules. Few, if any, will result in a viable antagonist. Such antagonists cannot be predicted, nor is there any teaching or suggestion, based on the cited references.

That the pending claims are directed to cytokines further complicates the situation. As cytokines are very complex molecules, there is more complexity to modifying the molecule and even less predictability in the types of products resulting from such modifications. The cited references simply provide no teaching or suggestion as to the types of products that can result from modifications, nor do they teach or suggest site specific modifications. Accordingly, with such complexity, one of ordinary skill in the art would simply have no expectation of success without undue experimentation. The claimed invention provides an elegant solution to dealing with complex molecules which was not taught or suggested by the cited references. It is certainly unexpected that one could introduce desirable new properties in molecules as complex as cytokines with the claimed method.

Claim 136 stands rejected under 35 U.S.C. § 103(a) as being obvious over Smit I in view of Smit II and further in view of U.S. Patent No. 4,511,502 to Builder et al. Applicant respectfully requests reconsideration and allowance in view of the remarks herein.

In regard to claim 136, the Examiner has used stated that it would be obvious use urea and EDTA in the method of Smit II even though neither Smit I nor Smit II teach using urea or EDTA. First, Applicant notes that the only modification in Smit I involves modification with proteases. Applicant respectfully submits that it is not obvious to use protease modification in combination with substances which prevent protease action. Such a combination would be non-sensical because protease modification of Smit I would be impaired by urea and EDTA.

In regard to Smit II, Applicant notes that no degradation was observed in any of the reactions. *See* page 252, right column, where it states "degradation of hIL-3 was excluded by SDS-electrophoresis." Indeed, Smit II also provides no teaching or suggestion that there were any insolubility problems. Accordingly, it would not be obvious to introduce substances which prevent protease action, degradation, or solubility problems.

Accordingly, Applicant respectfully submits that use of urea and EDTA was not obvious over either Smit I or Smit II because one of ordinary skill in the art would have no motivation to inhibit protease in a method directed to protease treatment (Smit I), nor would it be obvious to modify the method of Smit II when there is no teaching or suggestion of solubility or degradation problems.

Claims 94-111, 133, and 136-141 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 54-68 of copending Application No. 11/979,278.

Applicant respectfully submits that the invention claimed herein is patentably distinct over that claimed in the '278 application. Independent claim 54 of the '278 application is directed to a method for stimulating stem cell-replication. Such a method is not suggested by the inventions of pending claims 94-111, 133 or 136-141. Independent claim 56 is a product

claim directed to a modified signal substance. The pending claims herein are method claims. Accordingly, Applicant respectfully traverses the double patenting rejection.

Applicant respectfully requests entry of the present amendment, reconsideration, and withdrawal of the rejections to claims 94 to 111, 133, and 136 to 141, and this application passed to allowance. The Commissioner is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 06-1135.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

Dated: October 13, 2009

Kendrew H. Colton
Registration No. 30,368

One Lafayette Centre
1120 20th Street, N.W., Suite 750S
Washington, D.C. 20036
Telephone (202) 419-7000
Facsimile (202) 419-7007